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| EXAMINER | |
|---|---|
| TESKIN, R | |
| ART UNIT | PAPER NUMBER |
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DATE MAILED: 09/23/88

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-19 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-19 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.

8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).

10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.

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12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. ~~119~~. The certified copy has ☒ been received ☐ not been received
    ☐ been filed in parent application, serial no. _____; filed on _____.

☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

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EXAMINER'S ACTION

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless-

Claims 1 and 5 are rejected under 35 U.S.C. 101 because as being directed to products of nature.

Claims 1 and 5 because of the open claim language and also because X may encompass all of the amino acids between 760 through 1708 encompasses the native factor VIII≅c protein and the gene encoding this protein, which are products of nature and as such are unpatentable.

The disclosure is objected to because of the following informalities:

1) The specification does not contain a statement that the application is a CIP of 725,350.

2) The amino acid sequence depicted in table 1 should be in figure form.

Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to mammalian host cells capable of expressing factor VIII≅c in active form. See MPEP 706.03(n) and 706.03(z).

The specification only enabling expression of active factor VIII ≅ C in mammalian cells (CHO and COS cells exemplified) Absent evidence to the contrary it is questioned as to whether one of ordinary skill would be able to clone factor VIII:C in bacteria

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or yeast as claimed. For one thing, the protein may require proper glycosylation for activity which bacteria are incapable of, and yeast often do not glycosylate mammalian proteins, or if they do often the glycosylation pattern differs from that obtained in mammalian cells. Additionally the factor VIII ≅ C requires cleavage events for activity which may not occur in the bacterial or yeast cells. Also, the factor VIII ≅ C protein is very large and may not be recoverable in bacteria (may acculate as a refractive body), or may be proteolytically degraded by the yeast or bacterial cells, or may be toxic in these hosts.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

All of claims are indefinite and are objected to for their referral to a table. The intended sequence should either be set out in the claims, or alternatively the table should be put in figure form.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless-
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

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Claims 1, 5, 9-11 are rejected under 35 U.S.C. 102a as being anticipated by Wood et al.

Wood et al teach a DNA sequence encoding human factor VIII ≅ C, expression vectors containing the sequence, and transformed mammalian cells which secrete the factor VIII ≅ C protein in active form.

The protein expressed by Wood et al, DNA sequence encoding, and transformed mammalian cells which express the pretein anticipate these claims because of the open claim language "containing" and the fact that the X moiety may encompass all 949 resides between 760 and 1708 which includes factor VIII ≅ C sequences with no internal delections.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 12, 16 are rejected under 35 U.S.C. 103 as being unpatentable over Wood et al.

Absent any unexpected results, it would have been obvious to have utilized the recombinant factor VIII C taught by Wood et al in pharmaceutical compositions for treating hemophilia A, since it is taught to comprise procoagulant activity and it would be superior to factor VIII : obtained from natural serum sources in that it would be free from potential serum contaminants, e.g. viruses, other serum proteins.

Claims 6-8, 2-4 are rejected under 35 U.S.C. 103 as being unpatentable over Wood et al and Toole et al in view of Vehar et al.

Vehar et al teach the domain structure of human factor VIII:C. The domains are referred to as A, B and C with the A domain consisting of 3 triplicated seguences at positions 1-324, 380-711 and 1649-2019, the B domain separating second and third A domain and being rich in glycosy ation sites, and the C domain consisting of 150 duplicated amino acids at the C terminus of the molecule. The removal of the B domain or its fragments (see page 341 right hand column) by thrombin is speculated to result in the activation of aactor VIII=C. Probable thrombin cleavage sites which enable the removal of the B domain are identified at position 1649 (see left hand column page 338) and position 740 (see page 370 left hand column). The factor VIII molecule is taught to be very similar to the factor V coagulant (see paragraph

bridging pages 341-342). Among the similarities: (1) they are both proteins of ~300Kd; (2) they are both cleaved by thrombin (series of cleavage events ) resulting in 90 and 80 kda proteins Corresponding to the N and C termini of the native proteins) and (3) both comprise highly glycosylated internal domains which are cleaved from the protein upon proteolytic activation. Wood et al is discussed supra. Additionally, it is noted that Wood et al teach that the coagulant activity of native factor VIII:C is enhanced by incubation with thrombin resulting in prtcolytic cleavage. The fragments range in size from a set of 90-120 KD corresponding to the N terminus of the factor VIII molecule, and another set of 80 Kda corresponding to the C terminus of the mature factor VIII:C polypeptide (See page 366 under conclusion). The removal of the B domain (same B domain as in the Vehar et al reference) is taught to result in the activation of factor VIII:c.

Toole et al teach the cloning and expression of human factor VIII : C in the mammalian expression vector pCVSVL under the control of the adenovirus late promotor transfected COS-1 cells (see page 345). The recombinant polypeptide comprises detectible procoagulant activity.

The construction of CDNA encoding factor VIII:C, an expression vector comprising this CDNA, and

the transfection of mammalian cells with the vector for the production of active factor VIII: C would have been obvious as taught by Toole et al and Wood et al. Because of Wood et al disclosure that the proteolytic activation of factor VIII : C requires removal of an internal glycosylated domain (B domain) and further in view of Vehar et al who substantiate this finding and identify cleavage sites which permit the removal of this domain, it would have been obvious to have constructed CDNA's encoding factor VIII:C which lack the B domain, since it would be expected that they could be more easily expressed and isolated (because they would be smaller, and not comprise the heavily glycosylated poortion of the protein) and that they would result in active proteins since this domain is not required for activity.

Absent unexpected results, it is deemed that the determination as to which internal portions of the factor VIII:C may be deleted without loss of procoagulant activity, would have been determined by one or ordinary skill by claving sucessively larger internal deletions. Note that it is not unexpected that much of the internal portion of the protein can be deleted since it is taught by Wood et al that fragments of factor VIII:C of size as small as 90 and 80 KdD comprise procoagulant activity.

Claims 13-15. 17-19 are rejected under 35 U.S.C. 103 as being unpatentable over Toole et al and Wood et al in view of Vehar et al.

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The recombinant production of factor VIII$^{\circ}_{=}$C comprising an internal deletion correpsonding to the heavily glycosylated portion of the protein (B domain) would have been obvious over Toole et al and Wood et al in view of Vehar et al as applied to claims 2-4 and 6-8 supra. The use of the resulting modified factor VIII$^{\circ}_{=}$C in pharmaceutical compositions for treating haemophilia A is deemed to have been obvious since it would have been expected to comprise procoagulant activity and be superior to factor VIII: C obtained from serum sources in that it would be free of viral and other adverse serum contaminants.

Any inquiry concerning this communication should be directed to Examiner Teskin at telephone number 703-557-5996.

Teskin/ej

9-1-88

Robin Teskin

ROBIN TESKIN
EXAMINER
ART UNIT 127